REMARKS

Claims 1 to 13 and 15 to 62 are pending in the application. Claims 63 to 66 are newly added.

Reconsideration of the above-identified application in view of the amendments above and the remarks following is respectfully requested.

Claims 1-8, 11-13, 15-21, 23-31, 34, 35, 38-49, 51, 53, 55-57, 59, 61 and 62 are rejected under 35 USC 103(a) as being rendered obvious in light of Bacus et al U.S. Patent 6,101,265 in view of Kley U.S. Patent 4,806,776 and Engelhardt, U.S. Patent 6,529,271.

The claims are now amended to point out the feature disclosed in the registration and fine tuning embodiment described in relation to Fig. 4 of the present application. As explained in the application in the embodiment of Fig. 4, an image is taken of an object, typically mounted on a slide. An intrinsic or internal reference system is constructed based on features of the image. Those features may be geometric features such as the edge of the slide or they may be actual features of the object, which can be identified by state of the art image processing techniques.

Use of such an internal reference system allows subsequent changes to be made to the slide and for the changes not to interfere with the system's ability to re-register. Thus an image can be taken and then changes made to the object and a new image taken, or the same object can be imaged in different ways and the two images matched. This can be done using an ordinary microscope and without any effort in aligning the slide on the stage. The matching is carried out automatically, and is effective despite the changes being made to the image.

In order to illustrate the point, reference is now made to attached figures 1, 2 and 3. Each image shows the same area twice, under different conditions. In each image, the right side was taken first, with staining that shows cells-morphology, and under bright field illumination.

The left side of each image was taken several days later. In the meantime the slide had been removed from the microscope, the morphology-staining had been removed and genetic markers had been applied to the cells in its stead. Then the cells were placed on another microscope, using another objective and another illumination type, this time fluorescent illumination, and the system allowed the image to return exactly to the same location for the second image gathering process.

Although the first stain was completely removed, and the cells were physically changed (note the lack of cytoplasm in the fluorescent images), and although using the original imaging process will not show the cells at all, the system of the present embodiments allowed exact re-location of each and every cell on the sample.

Bacus et al, as discussed in the previous response, discloses imaging at low resolution over a relatively large area. The user finds a region of interest using a low resolution image, selects the region of interest using a marker or cursor and then is provided with a corresponding high resolution image of the region of interest. In the preferred embodiment the lower and higher resolution images are obtained using different power lenses on the same microscope. The imaging method is the same, and the only change is in the power of the lens used. As regards a co-ordinate system, Bacus does not use intrinsic co-ordinates of the object or of the image made from the object mounted on the slide. As clearly

stated in Bacus column 9 line 42, the co-ordinate system he uses are in fact X and Y co-ordinates of the microscope stage. This is sufficient for Bacus where the different images are simply the same mounting imaged with different magnification lenses. The slide is not moved in the meantime and therefore if the operator selects a point on the image taken from one magnification, the selected point is simply translated to the corresponding X-Y co-ordinates of the stage.

In the present invention however, the possibility is provided of moving the slide, imaging it using a different technique, restaining it and the like. The slide may be removed and then replaced on the stage in the meantime and may thus have moved with respect to its original position. The invention therefore provides a co-ordinate system which is intrinsic to the image. For example the corner of the slide might be used as an origin of the co-ordinate system. Consequently it makes no difference how carefully the slide is replaced on the stage.

In fact, making the co-ordinate system dependent on the image data including the slide, provides a further advantage. It means that the initial image can be taken on one microscope and the second image on another microscope. This is especially useful if the two imaging techniques cannot be carried out on the same microscope. The current art does not allow for integrated navigation between two images from different microscopes.

In the present invention, the co-ordinate system works *after* the slide has been *moved* and *replaced*, and *between two microscopes*. In Bacus the co-ordinate system does neither of these since the co-ordinate system is based on the *stage of the microscope*.

An example of two processes for which the co-ordinate system of the present invention is very helpful in matching between is as follows:

In a first imaging process, the specimen may be prepared using a fluorescent marker to obtain a fluorescent image giving morphological information of the specimen. In a subsequent imaging process a DNA marker may be applied and genetic information may be obtained from the same specimen. The morphological and genetic information may then be viewed side by side with matching over the two images using the intrinsic co-ordinate system. It is again stressed that neither Bacus nor any other of the prior art citations reveals how to co-ordinate between the two images because of movement between the two imaging processes or indeed their being imaged on two separate devices.

Thus the feature of the newly amended claim that the co-ordinate system is *intrinsic to the image* is not taught or even suggested in Bacus.

The above defined missing information is also not taught in Kley or in Engelhardt.

As discussed in the previous response, Kley discloses a system giving selectable illumination systems on a single microscope device for viewing an object under different desired illumination conditions. Kley therefore goes beyond Bacus in providing not just different resolution images of the same object, but images produced in different ways. However, because the images are produced in different ways, there is no integration between the different illumination systems. That is to say the different images produced are fully unconnected images and there is no attempt madc to select a co-ordinate in one image and find the same region on the next.

Engelhardt discloses a method of finding recording and optionally evaluating object structures, especially on slides, preferably of fluorescent feature structures such as gene spots. The disclosure teaches using illumination patterns to find features of interest and also teaches using two illumination sources simultaneously on the same

object. It does not however teach a co-ordinate system which allows a feature on one image to be found on a second image. It certainly does not teach a co-ordinate or any other kind of reference system which is intrinsic to the object or image.

It is thus submitted that neither Kley nor Bacus nor Engelhardt disclose the key point that image location data is gathered which is intrinsic to the image itself so that images from two different image gathering operations can be compared. Such a point is believed to be clearly claimed in claim 1 as amended.

In the present invention, the location data is gathered using intrinsic location data of the image based on the slide or the object itself, and is thus independent of the image gathering method or of the location of the slide on the stage as in Bacus. The prior art neither discloses nor hints at such a way of registering between two images of the same object.

Furthermore, a particularly preferred embodiment of the present invention can be applied to a standard microscope and does not require any special hardware.

As was pointed out in the previous response, in the field of microscopy it is common to carry out investigations simultaneously using different imaging methods. Navigating between the different images is a task that has for many years had to be carried out manually and has been the bane of many biological researchers. The invention of Kley, made in 1980, allowed for different illumination methods to be available on the same device, but did not include any integration between the images. There has been a long-felt want for a solution that allowed automatic navigation between the different images, and the hardware of Kley has existed for twenty three years, yet the application of the co-ordinate system of Bacus to the hardware of Kley would not arrive at a solution to this problem because as soon as the object is removed for restaining or the like, the stage based co-ordinate system of Bacus can no longer

register the images. There is no additional information in Engelhardt which allows this problem to be solved since Engelhardt does not mention any kind of co-ordinate system.

Corresponding amendments have been made to each of the other independent claims so that they all now define a co-ordinate or indexing system which is intrinsic to the object or the corresponding image data.

It is therefore concluded that the independent claims are both novel and inventive in light of the combination of Bacus Kley and Engelhardt and that the Examiner's objection is overcome.

The dependent claims are believed to be allowable as being dependent on allowable main claims.

Claims 9, 10, 22, 36 and 37 are rejected in light of the above combination of Bacus, Kley and Engelhardt and additionally in light of Trulson. It is respectively submitted that the combination of Bacus and Kley fails to teach the use of a co-ordinate system intrinsic to the object or the image data, as discussed above, and that therefore these claims are allowable.

Claims 32 and 50 are rejected over the combination of Bacus, Kley and Engelhardt and additionally in light of Spigarelli. It is respectively submitted that the combination of Bacus, Kley and Engelhardt fails to teach the use of a co-ordinate system intrinsic to the object or corresponding image, as discussed above, and that therefore these claims are allowable. Spigarelli is not concerned with imaging as such. Rather it discloses object location in order to control and manipulate the object using a robot arm. Thus while Spigarelli uses imaging to obtain a fix on the corners of an IC that it is intended to pick up it does not use that fix to generate any kind of intrinsic

reference system or indexing system for the interior of the object as required by the claims.

Claim 33 is rejected over the combination of Bacus, Kley and Engelhardt and additionally in light of Hellmuth. It is respectively submitted that the combination of Bacus Kley and Engelhardt fails to teach the use of a co-ordinate system intrinsic to the image or object, as discussed above, and that therefore these claims are allowable.

Claims 52, 54, 58 and 60 are rejected over the combination of Bacus, Kley, Engelhardt and Yamamoto. It is respectively submitted that the combination of Bacus and Kley fails to teach the use of a co-ordinate system independent of the imaging method, as discussed above, and that therefore these claims are allowable. In particular, Yamamoto does not teach how to apply one fluorescent die to an object, take an image, remove the object to apply another fluorescent die, replace the object, take another image and provide co-ordination between the two images. Yamamoto also does not teach how to proceed in the example given above where a first imaging process uses a fluorescent marker to obtain morphological information and then a second imaging process uses a DNA marker to obtain genetic data. Even if the co-ordinate system disclosed in Bacus were to be applied it would not work since Bacus teaches using the *co-ordinates of the stage* and the object has since been *moved in relation to the stage* or indeed the two images were made on *different stages* of different microscopes or other imaging devices.

New claims 63 – 67 have been added. Claim 63 to restaining is supported by the description of Fig. 4. The markers of claim 64 are discussed inter alia in the paragraph bridging pages 23 and 24. Contrast enhancement as in claim 65 is intrinsic to the stains discussed and the staining concept in general. FISH, as in claim 66, is to be found in the paragraph bridging pages 23 and 24.

All of the matters raised by the Examiner have been dealt with and the rejections are believed to have been overcome. Thus the application is believed to be in order for allowance.

In view of the above amendments and remarks it is respectfully submitted that all the pending claims are all now in condition for allowance. Prompt notice of allowance is respectfully and earnestly solicited.

Respectfully submitted,

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